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10/517,713	12/10/2004	Magnus Polla	056291-5268	9146

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EXAMINER	
OH, TAYLOR V	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,713	POLLA, MAGNUS	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 12* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The Status of Claims:

Claims 1-12 are pending.

Claims 1-7 and 12 are rejected.

Claims 9-11 are withdrawn from consideration

Claim 8 is objected.

DETAILED ACTION

1. Claims 1-8 and 12 are under consideration in this Office Action.

Priority

2. It is noted that this application is a 371 of PCT/SE03/00970 (06/10/2003).

Drawings

3. None.

Claim 8 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims 5-6. See MPEP § 608.01(n). Accordingly, the claim 8 has not been further treated on the merits.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-8 and 12) on 4/25/08.

Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected groups II, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-4, there are various types of the parentheses employed to describe many variables for the claimed compounds. These are vague and indefinite because the skilled artisan in the art is unable to figure out the metes and bounds of the claimed limitations. Therefore, an appropriate correction is required.

In claims 1 and 7, the symbols "I" and "R1R*" are recited. These are vague and indefinite because there is no definition for each of them. Therefore, an appropriate correction is required.

In claim 1 , the phrase " substituted phenyl " is recited. This is vague and indefinite because in the absence of the specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein

applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. Therefore, an appropriate correction is required.

In claim 7 , the phrase " a group that can be subsequently reacted to form R1R*" is recited. This is vague and indefinite because the skilled artisan in the art is unable to figure out how it is possible for" any group " subsequently to react to form R1R*" by any types of reagents without any definitive chemical structures. Therefore, an appropriate correction is required.

In claim 7 , the phrase " subsequently removing the protecting groups as necessary" is recited. This is vague and indefinite because the skilled artisan in the art is unable to figure out when it is time to remove the protecting groups as necessary. . Therefore, an appropriate correction is required.

Claim 12 provides for the use of the pharmaceutical composition, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are

drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State

Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing or prophylaxis of diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established

prophylactics are vaccines not the compounds of formula(I) such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before it occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning lines 22-26, page 26 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical trial medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become prevented before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in those diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the

prevention of those diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent those generally. That is, the skill is so low that no compound effective generally against any disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word “preventing of prophylaxis” and the phrase "reducing the risk".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A person shall be entitled to a patent unless –

Claims 1-7 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Linschoten et al (WO 00/66557).

Linschoten et al discloses the following compound (see page 86, example 31):

2-(6-Amino-pyridin-3-ylmethyl)-3-mercapto-5-phenyl-pentanoic acid

(a) Ethyl (*E,Z*)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenyl-2-pentenoate

To a suspension of NaH (310 mg, 7.12 mmol, 55% in mineral oil) in THF (25 mL) at 0°C under argon was added a solution of (ethyl 3-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-2-(diethoxyphosphoryl)propanoate (2.55 g, 5.95 mmol) in THF (25 mL). After 1 h, a solution of 3-phenylpropanal (1.59 g, 11.9 mmol) was added dropwise. The reaction was stirred for 17 h at room temperature, then quenched with NH_4Cl (50 mL, sat, aq). The mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 20:1 → 10:1) gave ethyl (*E,Z*)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenyl-2-pentenoate (2.49 g, 100%).

(b) Ethyl 3-(acetylsulfanyl)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenylpentanoate

Triethylamine (1.22 mL, 0.617 mmol) was added to a solution of ethyl (*E,Z*)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenyl-2-pentenoate (400 mg, 0.597 mmol) in thioacetic acid (10 mL) at 40°C. After stirring for 90 h., the mixture was concentrated under reduced pressure. Column chromatography (CH_2Cl_2/EtOAc 20:1 → 10:1), then (toluene/EtOAc, 10:1) and then (heptane/EtOAc 2:1) gave ethyl 3-(acetylsulfanyl)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenylpentanoate (126 mg, 27%) as a diastereomeric mixture 1:1.

(c) 2-(6-Amino-pyridin-3-ylmethyl)-3-mercapto-5-phenyl-pentanoic acid

Ethyl 3-(acetylsulfanyl)-2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-5-phenylpentanoate (9 mg, 18.5 µmol) was dissolved in conc. HCl (1 mL) under argon. The solution was heated to reflux for 4.5 h. Concentration under reduced pressure yielded the title compound as the hydrochloride salt (6.4 mg, 98 %) as a diastereomeric mixture 1:1.

This is identical with the claims.

Allowability

The elected species below:

2-[(6-aminopyridin-3-yl)methyl]-5-(3-chlorophenyl)-3-mercaptopentanoic acid

is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Taylor Victor Oh, MSD,LAC
Primary Examiner
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5/24/08